REMARKS

In the Office Action dated August 27, 2003, claims 1-17 are pending and under consideration. The specification is objected to for allegedly failing to comply with the Sequence Rules. Claims 1-17 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 1-17 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Van der Zee et al. (U.S. Patent No. 5,684,145) and Zhu et al. (*Vaccine*, 1996; 14 (1): 61-69).

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

The specification is objected to for allegedly failing to comply with the Sequence Rules. The Examiner points to a specific example in the specification on page 2, lines 3 and 5.

Applicants have amended the specification to insert the corresponding sequence identifier for the sequence disclosed on page 2, line 3. Applicants have also deleted the sequence disclosed on page 2, line 5, which is essentially a derivative of the sequence disclosed on page 2, line 3, and is already defined by the sentence preceding the deleted sequence. Therefore, the amendment to the specification does not introduce new matter and obviates the Examiner's objection. Withdrawal of the objection is therefore respectfully requested.

Claims 1-17 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner contends that the recitation "synergistically affects the first proteinaceous portion by enhancing inhibition activity of the peptide that is analogous to said first proteinaceous portion", which was introduced in the previous amendment to claims 1 and 3, is not supported by the specification and is new matter.

Applicants respectfully submit that claims 1-17 have been canceled by the instant amendment, rendering the rejection thereof moot. The objected-to recitation is not present in new claims 18-35. Therefore, the rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 1-17 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Van der Zee et al. (U.S. Patent No. 5,684,145) and Zhu et al. (*Vaccine*, 1996; 14 (1): 61-69).

Applicants respectfully submit that the rejection of claims 1-17 is rendered moot in view of cancellation of these claims. Withdrawal of the rejection is therefore respectfully requested. Applicants further submit that new claims 18-35 are not obvious in view of Van der Zee et al. and Zhu et al.

In the first instance, Applicants respectfully submit that claims 18-21 are drawn to a fusion protein producing a dual immune response in a vertebrate, which comprises a first proteinaceous portion relating to GnRH, the activity of this peptide is to be inhibited within the vertebrate; and a second portion relating to the immunogenic glycoprotein D (gD) from BHV-1. Claims 22-26 are directed to nucleic acid molecules encoding such fusion protein, and the related vectors and host cells. Claims 27, 30 and 33 are drawn to dual-function vaccines that comprise a fusion protein, a vector or a transformed cell that inhibits the activity of endogenous GnRH (including inhibiting the sexual characteristics in a cow) and protects against BHV-1. Claims 28-29, 31-32 and 34-35 are directed to methods relating to the use of the dual-function vaccines. Support for claims 18-35 is found in original claims 1-17, and in the specification, e.g., at page 16, lines 29-30; page 17, lines 16-32; and page 40, line 14 through page 41, line 2.

Van Der Zee et al. teach a recombinant DNA molecule that codes for a hybrid protein comprising GnRH that is conjugated to *E. coli* fimbrial-filiments in a vaccine that elicits an

immune response against GnRH. Zhu et al. teach inducing mucosal and systemic immunity against BHV-1 using glycoprotein D (gD) of BHV-1.

The Examiner contends that one skilled in the art would have been motivated to substitute the *E. coli* P-fimbrial subunit portion of the hybrid protein of Van Zee et al. with the strongly immunogenic BHV-1 gD of Zhu et al. to evoke an immune response against GnRH and against BHV-1. The Examiner also contends that one skilled in the art would have had a reasonable expectation of success in producing the claimed invention, allegedly because Van Der Zee et al. indicate that *all that is needed to induce an immune response against GnRH is a strong immunogenic carrier* (see columns 1-5 of Van der Zee et al.), which is what gD from BHV-1 is. Further, the Examiner states that it is conventional practice in the vaccine arts to incorporate highly antigenic glycoproteins into a vaccine. Therefore, the Examiner concludes that it would have been obvious to one skilled in the art to substitute gD of BHV-1 for the *E. coli* fimbrial-filiments in the hybrid protein taught by Van Der Zee.

Applicants respectfully submit that the rejection of claimed subject matter under 35 U.S.C. §103 in view of a combination of prior art references requires that the suggestion to carry out the claimed invention must be found in the prior art, *not in Applicant's disclosure.* In re Vaeck, 947 F.2d 488, 492, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991). In the instance case, the suggestion to make a conjugated protein of GnRH and gD appears nowhere in either of the cited references.

More specifically, Van Der Zee et al. do not suggest making a conjugated protein of GnRH and gD. Van Der Zee et al. merely teach making a hybrid protein comprising GnRH that is conjugated to *E. coli* fimbrial-filiments, which conjugated protein purportedly elicited an immune response in a recipient against GnRH. There is no indication in Van der Zee et al. that

the results achieved therein with GnRH conjugated with fimbrial-filiments, can be extrapolated to GnRH conjugated to other protein carriers. In fact, Van der Zee et al. teach the contrary.

Specifically, Van der Zee et al. describe at col. 2, lines 50-60, that conjugation of GnRH to other protein carriers, such as bovine or human serum albumin, tetanus toxoid or thyroglobulin, resulted in poorly defined immunogens that did not retain all structural features of GnRH for generating antibodies capable of blocking the function of GnRH. Van der Zee et al. also refer to a hybrid protein of GnRH conjugated with a short peptide, which generated antibodies that do not have any effect on the biological activity of GnRH. See col. 3, lines 3-20. Even with *E. coli* fimbrial subunits, not all conjugates evidenced success. For example, Van der Zee et al. describe that DNA coding for a P-fimbrial filament with an insertion of GnRH in HR1 of the major subunit of a P-fimbrial filament was discovered to be practically incapable of fimbriae formation. See col. 4, lines 64-67 of Van der Zee et al. Van der Zee et al. therefore consider it to be a *surprising* discovery that a conjugated protein containing an antigenic determinant of GnRH inserted in the HR4 region of the major subunit of a fimbrial filament resulted in good fimbriae formation and gave good exposure of the antigenic determinant of GnRH, which led to an *unexpectedly* high titer of antibodies against GnRH so as to have an effect on the function of GnRH.

Therefore, contrary to the Examiner's allegation that Van der Zee et al. at col. 1-5 teach that all that is needed to induce an immune response against GnRH is a strong immunogenic carrier, Applicants respectfully submit that the teachings of Van der Zee et al. are limited to the specific conjugate of GnRH inserted in the HR4 region of the major subunit of a fimbrial filament. Van der Zee et al. do not teach or suggest, and in fact teach away from, the

notion that GnRH can be conjugated with any immunogenic carrier, let alone BHV-1 gD, in order to evoke an immune response capable of inhibiting the activity of GnRH.

The secondary reference, Zhu et al., simply characterizes the BHV-1 gD protein. Zhu et al. do not teach or suggest making a conjugated protein of GnRH and gD.

Therefore, the cited references, viewed individually or in combination, fail to provide the requisite suggestion achieve the claimed invention. Even assuming, *pro arguendo*, a suggestion is made by the combination of the cited references, Applicants respectfully submit that one skilled in the art would not have had a reasonable expectation of success.

The Examiner has argued that a reasonable expectation of success for producing the instant protein fusion is found in the cited references. Specifically, the Examiner states that Van der Zee et al. teach fusing GnRH and maintaining structural and functional epitopes required to induce an immune response against the protein in a fusion construct. The Examiner further states that one skilled in the art would also know the structural and functional epitopes of BHV-1 gD that must be maintained to induce the protective immunity, as evidenced by Zhu et al. (1996, *supra*), Zhu et al. (*Vaccine*, January 21, 1999; 17: 269-282) and Van Druden Little-Van den Hurk et al. (Virology, 1985; 144:216-227).

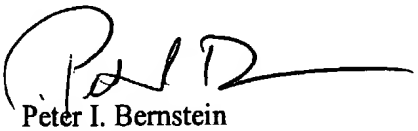
Applicants recognize that Zhu et al. (1996), Zhu et al. (1999) and Van Druden Little-Van den Hurk et al. may have provided certain characterization of the antigenic epitopes of BHV-1 gD. However, the only gD-conjugated protein disclosed is the gD-IL-6 conjugate in Zhu et al. (1999). Unlike the GnRH peptide of 10 amino acids in length, IL-6 is a protein of 208 amino acids that is immunogenic on its own, and was conjugated with gD by Zhu et al. (1999) to confer adjuvanticity on gD. The disclosure of Zhu et al. (1999) would not have provided one skilled in the art any reasonable expectation of success in obtaining a conjugate between gD and

a smaller peptide comprising one or several GnRH sequence, that would give sufficient exposure of the peptide to evoke an immune response strong enough to inhibit the function of GnRH *in vivo*.

In sum, Applicants respectfully submit that the cited references, alone or in combination, do not teach or suggest making a GnRH-gD conjugate, as presently claimed. Furthermore, one skilled in the art would not have had a reasonable expectation of success that such a conjugate, if made, would be capable of provoking an immune response that inhibits the function of GnRH *in vivo*, as presently claimed.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Peter I. Bernstein
Registration No. 43,497

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
Telephone: 516-742-4343

XZ:ab/lf